elicited after HCV infection [Farci et al., *Science* **258**, 135-140 (1992); Prince et al., *J. Infect Dis.* **165**, 438-443 (1993)] present major challenges towards these goals.—

In The Claims:

Please amend the claims as indicated:

Cancel claims 10, 11, 18-24, 41-44 and 63-68.

1. (Four times amended) A polynucleotide comprising a non-naturally occurring HCV sequence that is capable of productive replication in a host cell, or is capable of being transcribed into a non-naturally occurring HCV sequence that is capable of productive replication in a host cell, wherein the HCV sequence comprises, from 5′ to 3′ on the positive-sense nucleic acid, a functional 5′ non-translated region (5' NTR); one or more protein coding regions, including at least one polyprotein coding region that is capable of replicating HCV RNA; and a functional HCV 3′ non-translated region (3' NTR), wherein said polynucleotide further comprises an adaptive mutation in the NS5A coding region that confers improved cell culture characteristics to said polynucleotide.

~~12~~ 9. (Amended) The polynucleotide of claim [11] 1, wherein the mutation is within 50 nucleotides of an interferon sensitivity determining region (ISDR) or includes the ISDR.

Rule 126 ~~24~~ 76. (New) The polynucleotide of claim 1, further comprising a mutation in the NS3 or NS4B coding region.

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